## REMARKS

The Examiner indicated that several sequences were without the required sequence identifiers, i.e., on pages 6-7, Table 5, and Claim 25. Applicants have made the appropriate corrections. Figures 2A and 2B are submitted by way of the Transmittal of Submission of New Drawings. Figure 2 contains data from deleted Table 5 (page 24, lines 1-45). Applicants believe that no new matter is added by way of amendment.

Respectfully submitted,

Date: April 8, 2002

By: _____
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Enclosed:

Copy of Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequence

Transmittal with new drawings, FIGS. 2A and 2B.

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the specification:**

The paragraph beginning on page 6, lines 4-37, and continuing to page 7, lines 1-15, has been amended as follows:

Certain polypeptide embodiments include an isolated or recombinant polypeptide that: A) specifically binds polyclonal antibodies generated against a 12 consecutive amino acid segment of SEQ ID NO: 2; and comprises at least one sequence selected from [(see SEQ ID NO: 2)]: LeuCysPheArgMetLysAsp (residues 8-14 of SEQ ID NO:2); ValLeuTyrLeuHisAsn (residues 19-24 of SEQ ID NO:2); GlnLeuLeuAlaGly (residues 26-30 of SEQ ID NO:2); IleSerValValProAsn (residues 43-48 of SEQ ID NO:2); SerProValIleLeuGlyVal (residues 56-62 of SEQ ID NO:2); GlnCysLeuSerCysGlyThr (residues 67-73 of SEQ ID NO:2); ProIleLeuLysLeuGlu (residues 77-82 of SEQ ID NO:2); PheTyrArgArgAspMetGly (residues 101-107 of SEQ ID NO:2); LeuThrSerSerPheGluSer (residues 108-114 of SEQ ID NO:2); PheLeuCysThrSer (residues 121-125 of SEQ ID NO:2); GlnProValArgLeuThr (residues 130-135 of SEQ ID NO:2); PheTyrPheGlnGln (residues 150-154 of SEQ ID NO:2); ArgAlaLeuAspAlaSerLeu (residues 49-55 of SEQ ID NO:2); or GlyLeuHisAlaGluLysVal (residues 31-37 of SEQ ID NO:2); or B) specifically binds polyclonal antibodies generated against a 12 consecutive amino acid segment of SEQ ID NO: 6, 13, or 15; and comprises at least one sequence selected from [(see SEQ ID NO: 6)]: SerLeuArgHisValGlnAsp (residues 13-19 of SEQ ID NO:6); ValTrpIleLeuGlnAsn (residues 24-29 of SEQ ID NO:6); IleLeuThrAlaVal (residues 31-35 of SEQ ID NO:6); IleThrLeuLeuProCys (residues 46-51 of SEQ ID NO:6); AspProThrTyrMetGlyVal (residues 63-69 of SEQ ID NO:6); SerCysLeuPheCysThrLys (residues 74-80 of SEQ ID NO:6); ProValLeuGlnLeuGly (residues 85-90 of SEQ ID NO:6); PheTyrHisLysLysSerGly (residues 109-115 of SEQ ID NO:6); ThrThrSerThrPheGluSer (residues 116-122 of SEQ ID NO:6);

PhelleAlaValCys (residues129-133 of SEQ ID NO:6); CysProLeuIleLeuThr (residues 138-143 of SEQ ID NO:6); PheGluMetIleVal (residues 154-158 of SEQ ID NO:6); GlnAspLeuSer (residues 18-21 of SEQ ID NO:6); ValProArgLysGluGlnThrVal (residues 35-42 of SEQ ID NO:6); SerLysGlySerCysPro (residues 134-139 of SEQ ID NO:6); ArgAlaAlaSer (residues 8-11 of SEQ ID NO:6); ProCysGlnTyrLeuAspThrLeuGlu (residues 50-58 of SEQ ID NO:6); and SerGlyThrThr (residues 114-117 of SEQ ID NO:6); or [(see SEQ ID NO: 13 or 15)] ITGTIND (residues 23-29 of SEQ ID NO:13); VWTLQG (residues 34-39 of SEQ ID NO:13); NLVAV (residues 41-45 of SEQ ID NO:13); VAVITC (residues 56-61 of SEQ ID NO:13); DPIYLGI (residues 73-79 of SEQ ID NO:13); MCLYCEK (residues 84-90 of SEQ ID NO:13); PTLQLK (residues 95-100 of SEQ ID NO:13); FYRAKTG (residues 119-125 of SEQ ID NO:13); RTSTLES (residues 126-132 of SEQ ID NO:13); FIASS (residues 139-143 of SEQ ID NO:13); QPIILT (residues 147-152 of SEQ ID NO:13); FELNI (residues 163-167 of SEQ ID NO:13); SMCK (residues 18-21 of SEQ ID NO:13); NDLN (residues 28-31 of SEQ ID NO:13); [VPR(R/S)TSVT] VPRRTSVT (residues 45-51 of SEQ ID NO:13); [VPRSDSVT;] TCKYPEALE (residues 60-68 of SEQ ID NO:13); TGRT (residues 124-127 of SEQ ID NO:13); [SKRDQP;] or SKGDQP (residues 143-148 of SEQ ID NO:13), or VPRSDSVT (residues 45-52 of SEQ ID NO:15); SKRDQP (residues 143-148 of SEQ ID NO:15). Preferred embodiments include such a polypeptide: wherein the polypeptide comprises a plurality of the described sequences. Preferably the 12 consecutive amino acid segment comes from an IL-1δ sequence (see SEQ ID NO: 2): LeuCysPheArgMetLysAspSerAlaLeuLysValLeuTyrLeuHisAsnAsn (residues 8-25 of SEQ ID NO:2); IleSerValValProAsnArgAlaLeuAspAlaSerLeuSerProValIleLeuGlyValGln (residues 43-63 of SEQ ID NO:2); SerProValIleLeuGlyValGlnGlyGlySerGlnCys (residues 56-68 of SEQ ID NO:2); ProIleLeuLysLeuGluProValAsnIleMetGluLeu (residues 77-89 of SEQ ID NO:2); ThrSerSerPheGluSerAlaAlaTyrProGlyTrpPhe (residues 109-121 of SEQ ID NO:2); PheLeuCysThrSerProGluAlaAspGlnProVal (residues 121-132 of SEQ ID NO:2); ThrGlnIleProGluAspProAlaTrpAspAlaProIle (residues 135-147 of SEQ ID NO:2); or ThrSerSerPheGluSerAlaAlaTyrProGlyTrpPhe (residues 109-121 of SEQ ID

NO:2); or a rodent IL-1ε sequence (see SEQ ID NO: 6): ArgAlaAlaSerProSerLeuArgHisValGlnAspLeu (residues 8-20 of SEQ ID NO:6); SerSerArgValTrpIleLeuGlnAsnAsnIleLeu (residues 21-32 of SEQ ID NO:6); ProValThrIleThrLeuLeuProCysGlnTyrLeu (residues 43-54 of SEQ ID NO:6); GlyValGlnArgProMetSerCysLeuPheCysThr (residues 68-79 of SEQ ID NO:6); PheCysThrLysAspGlyGluGlnProValLeuGlnLeu (residues 77-89 of SEQ ID NO:6); ThrSerThrPheGluSerAlaAlaPheProGlyTrpPhe (residues 117-129 of SEQ ID NO:6); or CysSerLysGlySerCysProLeuIleLeuThrGln (residues 134-144 of SEQ ID NO:6); or a primate IL-1ε sequence (see SEQ ID NO: 13 or 15): SMCKPITGTINDL (residues 18-30 of SEQ ID NO:13); NQQVWTLQGQNL (residues 31-42 of SEQ ID NO:13); PVTVAVITCKYP (residues 53-64 SEQ ID NO:13); GIQNPEMCLYCE (residues 78-89 of SEQ ID NO:13); YCEKVGEQPTLQL (residues 87-99 of SEQ ID NO:13); TSTLESVAFPDWF (residues 127-139 of SEQ ID NO:13); SKGDQPIILTSE (residues 143-154 of SEQ ID NO:13); SKRDQPIILTSE (residues 143-154 of SEQ ID NO:15);or GKSYNTAFELNIND (residues 156-169 of SEQ ID NO:15).

The paragraph on page 13, lines 3-11, has been amended as follows:

Figure 1A is a cartoon depicting a top down view through the central axis of the predicted IL-1δ or IL-1ε protein demonstrating the characteristic tertiary ß-trefoil structure with its 3-fold symmetric topology. Contact sites of the IL-1δ or IL-1ε protein that are predicted to bind the IL-1 receptor subunits are designated as sites A, B or C [(Table 5)] (Fig. 2). Contact sites A and C bind to the first receptor subunit of IL-1, while contact site B binds to the IL-1 second receptor subunit.

The paragraph on page 16, lines 21-22 has been amended as follows:

Table 4 shows relationship of IL-1 family members, and [Table 5] Fig. 2 provides an alignment of selected family members.

The paragraph on page 40, lines 16-30, has been amended as follows:

The present invention particularly provides muteins which act as agonists or antagonists of the IL-1δ or IL-1ε. Structural alignment of mouse IL-1δ and mouse IL-1ε with other members of the IL-1 family show conserved features/residues, particularly 12 β strands folded into a β-trefoil fold (see Fig 1A; Table 3 and [Table 5] Fig.2A,B). The 12 mouse IL-1δ β strand domains are recited respectively (Table 3) as Leu8-Asp14, Val19-Asn24, Leu27-Gly31, Ile43-Asn48, Ser56-Val62, Gln67-Thr73, Pro77-Glu82, Phe99-Met106, Leu108-Ser114, Phe121-Ser125, Gln130-Thr135, and Gln153-Asp156 of SEQ ID NO: 2; while the 12 mouse IL-1ε β strand domains are recited respectively (Table 3) as Ser13-Asp19, Val24-Asn29, Ile31-Val35, Ile46-Cys51, Asp63-Val69, Ser74-Lys80, Pro85-Gly90, Ser107-Ser114, Thr116-Ser122, Phe129-Cys133, Cys138-Thr143, and Ile157-His160 of SEQ ID NO: 6).

The paragraph on page 40, lines 31-37 and continuing to page 41, lines 1-2, has been amended as follows:

Alignment of the mouse IL-1δ and IL-1ε sequences (using the [met] Met initiation residue as the first amino acid) with other members of the IL-1 family indicates that the β conformations correspond to similar sequences in other IL-1 family members (see Tables 3, 4, and [5] Fig.2A,B). See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 263:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein Engineering 4:263-269.

The paragraph on page 42, lines 7-14, has been amended as follows:

The corresponding location in rodent IL-1δ or IL-1ε (between β4 and β5) defines a domain that forms a polypeptide loop which is part of a primary binding segment to the IL-1 receptor type (site B in [Table 5] Fig.2A,B). The loop, depicted

pictorially in Figure 1A as protruding into the central axis of the mature IL-1δ or IL-1ε protein, is located between arrows 4 and 5). More precisely, the loop is defined for IL-1δ by amino residues Pro47-Ala53 of SEQ ID NO: 2 and for IL-1ε by amino residues Pro50-Glu58 of SEQ ID NO: 6. Accordingly, IL-1δ or IL-1ε antagonist activity should be generated by removal all or an appropriate portion of a corresponding portion of amino acids located between β4 and β5. This suggests that analogous modifications to the loop between the β4 and the β5 strands will lead to variants with predictable biological activities. With mouse IL-1RA, it was shown that replacement of the mouse IL-1RA residues with those mouse IL-1β residues introduced IL-1 activity to the IL-1RA variant(IL-1RA could then bind type III receptor). Similar substitutions will establish that type III receptor can probably be used by mouse IL-1δ or IL-1ε proteins or muteins. Additional site B contacts are defined in rodent IL-1δ by amino residues 8-11, 13, 112, 114-117, 158 and 160 of SEQ ID NO: 2. Corresponding additional site B contacts are defined in mouse IL-1ε by amino residues 3-6, 8, 104, 106-109, 154 and 156 of SEQ ID NO: 6. Corresponding residues should be important in the primate sequence (see SEQ ID NO: 13 and 15).

The paragraph on page 42, lines 35-36 and continuing to page 43, lines 1-10, has been amended as follows:

Sites A and C (see [Table 5] Fig. 2A,B) mediate binding of IL-1δ or IL-1ε to the first IL-1 receptor subunit, e.g., an alpha receptor subunit. Site A contacts correspond in IL-1δ to amino residues 13-16, 22-24, 29, 31-37, 39, 126-131, 151, and 153 of SEQ ID NO: 2; while site C contacts correspond in IL-1δ to amino residues 74-98 of SEQ ID NO: 2. Site A contacts are defined in IL-1ε by amino residues 18-21, 21-29, 33, 35-42, 134-139, 155, and 157 of SEQ ID NO: 6; while site C contacts correspond in IL-1ε to amino residues 81-106 of SEQ ID NO: 6. Corresponding residues should be important in the primate sequence (see SEQ ID NO: 13 and 15).

**In the claims:**

25. (Amended Once) The binding compound of claim 24, wherein said 12 consecutive amino acid segment is selected from:

(1) LeuCysPheArgMetLysAspSerAlaLeuLysValLeuTyrLeuHisAsn-Asn (residues 8-25 of SEQ ID NO:2);

(2) IleSerValValProAsnArgAlaLeuAspAlaSerLeuSerProValIle-LeuGlyValGln (residues 43-63 of SEQ ID NO:2) [:];

(3) SerProValIleLeuGlyValGlnGlyGlySerGlnCys (residues 56-68 of SEQ ID NO:2);

(4) ProIleLeuLysLeuGluProValAsnIleMetGluLeu (residues 77-89 of SEQ ID NO:2);

(5) ThrSerSerPheGluSerAlaAlaTyrProGlyTrpPhe (residues 109-121 of SEQ ID NO:2);

(6) PheLeuCysThrSerProGluAlaAspGlnProVal (residues 121-132 of SEQ ID NO:2);

(7) ThrGlnIleProGluAspProAlaTrpAspAlaProIle (residues 135-147 of SEQ ID NO:2); or

(8) ThrSerSerPehGluSerAlaAlaTyrProGlyTrpPhe (residues 109-121 of SEQ ID NO:2).

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/770,528 | 01/25/2001 | Joseph A. Hedrick | DX0725K2B | 7799 |

7590 03/06/2002

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OIPE JC14A APR 16 2002 PATENT & TRADEMARK OFFICE

| EXAMINER | |
|---|---|
| KEMMERER, ELIZABETH | |
| ART UNIT | PAPER NUMBER |
| 1646 | 8 |

DATE MAILED: 03/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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DATE MAILED:

**Please find below a communication from the EXAMINER in charge of this application**
Commissioner of Patents

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D., whose telephone number is (703) 308-2673. The examiner can normally be reached on Mondays through Thursdays from 6:30 a.m. to 4:00 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached on (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

Elizabeth C. Kemmerer, Ph.D.
March 5, 2002

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Application No.: 09/[illegible],528

# NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

[X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

[ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

[ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

[ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

[ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

[ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

[X] 7. Other: The application discloses several sequences without the required reference to the relevant sequence identifiers. For example, claim 25 recites numerous peptide sequences without reference to a sequence identifier. It appears that these may be fragments of a longer sequence already listed in the application. If so, the claims may be amended to recite (residues x to y of SEQ ID NO: N) in order to comply with the sequence rules. Also, numerous fragments are disclosed at pp. 6-7 of the specification with a general reference to a longer sequence of which they are a part. This is insufficient. For each peptide, reference must be made to the amino acid residues from the longer sequence (such as in the format given above, or the format used at p. 90 of the instant specification). Finally, Table 5 discloses eight sequences without the required reference to the relevant sequence identifier.

## Applicant Must Provide:

An amendment to the application providing the required references to the relevant sequence identifiers.

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

**PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE**

OIPE JC14 APR 16 2002 PATENT & TRADEMARK OFFICE

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Date: Apr. 18, 2002 By: _____
Lois E. Miller

**PATENT**

Attorney Docket No.
DX0725K2B

CN 028008

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Joseph A. HEDRICK, et al.

Serial No.: 09/770,528

Filed: January 25, 2001

For: MAMMALIAN CYTOKINES; RELATED REAGENTS AND METHODS

Examiner: Elizabeth Kemmerer

Art Unit: 1646

Submission of New Drawings

Palo Alto, California 94304

April 8, 2002

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BOX: SEQUENCE
Honorable Assistant Commissioner for Patents
Washington, D.C. 20231

Honorable Sir:

In connection with the response to "Notice to Comply" with sequence listing requirements dated March 6, 2002, and the preliminary amendment filed herewith, enclosed please find new drawings FIG. 2A and FIG. 2B.

These drawings are a depiction of the material previously contained in table 5, found on page 25, beginning at line 11, of the specification and as such contains no new matter

Each sheet of these drawings has identifying indicia in the top margin of the drawing. If any of the formal drawings submitted are not in compliance, Applicants request an opportunity to correct any defects.

Respectfully submitted,

April 8, 2002

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